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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/126,559	07/30/1998	DANIEL J. CAPON	50130-E/JPW/	9053

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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	19

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/126,559	CAPON ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,8,55 and 57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,8,55, and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

1. In the Amendment filed August 2, 2002 (Amend. F), the applicant cancelled claims 37, 40, 56, and 58, and amended claims 1, 8, 55, and 57. Currently, claims 1, 4, 8, 55, and 57 are pending and under examination in the case.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. **(Prior Rejection-Withdrawn)** Claims 1, 4, 8, 55, and 57 were rejected in the prior action (mailed January 28, 2002) under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The grounds for this rejection were that the applicant failed to correlate the results of the claimed assay to the determination of the susceptibility of hepatitis C viral replication to a drug. In view of the applicants amendments to the claims in Amend. F, the rejection is withdrawn.

5. **(New Rejection- Necessitated by Amendment)** Claims 1,4, 8, 55, and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are described generally above. The claims are being rejected for enablement because it is not clear from the claims if the levels of expression of the indicator gene being measured and compared are levels of expression of the indicator gene as in the same host cell, and wherein the expression of the indicator gene is dependant on the patient-derived segment comprising a HCV gene. As the claim is unclear, for the purposes of this rejection, the clam is being interpreted as thought the levels of expression of the indicator gene are being compared alternatively in different cells, or with the indicator gene not being dependant on the HCV gene. In either case, the claim is rejected for lack of enablement because it is not known what effect either change will have on the levels of expression of the indicator gene independent of the removal of the drug.

6. **(New Rejection- Necessitated by Amendment)** Claims 1,4, 8, 55, and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims describe a method of assaying the susceptibility of hepatitis C viral replication to an anti-HCV drug. The claim is rejected step (c) the claim is unclear. This step reads "comparing the expression of the indicator gene as measured in step (b) with the expression of the indicator gene measured in the host cell of step (a) cultured in the absence of the anti-hepatitis C virus drug." It

is unclear from this language if the expression of the indicator gene being compared with the expression measured in step (b) is a comparison of the indicator gene expression while in the same cell or in another cell. I.e.: it is unclear if the reference to (a) is an identification of the indicator gene alone, or an indication that step (a) is being repeated except that the cell is being cultured in the absence of the anti-viral drug. It is suggested that an addition step of culturing and measuring be added prior to the step of comparison to more clearly identify what is being compared.

7. **(New Rejection- Necessitated by Amendment)** Claims 55 and 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Each of these methods involves the methods for determining resistance to anti-HCV drugs. These claims are indefinite for two reasons. First, the claims are indefinite because it is unclear from the claims if the methods are being conducted in vivo or in vitro. The claims state that they are testing the resistance to drugs "in a patient," thereby indicating an in vivo test. However, the claims are also dependant on claim 1, which is an in vitro test. Therefore, the claims are indefinite in that it is unclear if the methods are in vivo are in vitro.

Lastly, the claims are also indefinite in that, while describing step (a) of the method, they state "determining in the patient the susceptibility to an anti-hepatitis C virus drug at first time according to the method of claim 1..." It is unclear what purpose the reference to the method of claim one is intended to achieve. The method of claim 1 describes two measurements of the effects of an anti-HCV drug on the viral replication in a host cell. The methods of neither claim

55 nor claim 57 involve host cells or viral replication. Both of these later claims are concerned with the resistance of a patient to an anti-hepatitis C virus drug, and nowhere indicate a concern for viral replication. As there is no link between the method of claim 1 and the methods of claims 55 and 57, it is not clear why these later claims refer back to the method of claim 1. Further, if the reference to claim 1 is intended to help identify what is meant by "a first time point," the claim remains indefinite as there a no time points identified in claim 1: i.e. claim 1 lacks antecedent basis for the term "a first time point".

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. **(Prior Rejection- Withdrawn)** Claims 1, 4, 8, 55 and 57 were rejected in the prior action under 35 U.S.C. 103(a) as being unpatentable over Capon et al, in view of Lu et al, and Wang et al. In view of the applicant's statement that the current application and the Capon et al reference were either commonly owned, or subject to obligation of assignment to the same person, at the time of invention, thereby removing Capon et al. as a reference under #% U.S.C. 103(a), the rejection is withdrawn.

10. **(New Rejection)** Claims 1, 4, 8, and 57 are rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over U.S. Patent Number 6,127,116, issued to Rice et al. Claim1 describes a method of determining the susceptibility of hepatitis C viral replication to an anti-HCV drug comprising (a) culturing a host cell comprising a vector comprising a patient-derived segment of HCV and an indicator gene dependant upon the expression of the HCV segment both in the presence of, and without an anti-HCV drug; (b) measuring the expression of the indicator gene in each case; and (c) comparing the expression levels such that an increase in expression in the absence of the drug indicates that HCV replication is susceptible to the drug. Claim 4 further requires that the vector comprise a gene encoding one of several HCV proteins, wherein one of the potential proteins is NS4.

Rice teaches the making of DNA clones for HCV, and the use of such clones for diagnostic purposes, including use in methods to determine the effect of known or novel therapeutics on HCV replication. Abstract; and col. 38, lines 9-44. Rice teaches that there is a good deal of generic variability in HCV. Col. 7, lines 38-63. Therefore, the patents teaches the use of, or shows that it would have been obvious to one of ordinary skill in the art to use, HCV derived from a particular patient to ensure the anti-HCV drug being tested would be effective against the particular HCV with which that person was infected. Rice then goes on to teach that the nucleic acids of the HCV clones may have heterologous genes inserted into the clone with such genes operatively associated with expression control sequences. Col. 10, lines 50-65; and col. 11, lines 40-42. Rice indicates that such heterologous genes may be a reporter gene or encode marker proteins. Col. 10, lines 59-60, and col. 14, lines 17-24. The patent identifies several types of transcription and translational control sequences that may be used to control

expression of the HCV clone and accompanying heterologous sequence. Col. 23, lines 41-52. Among these control sequences, the patent included IRES elements (identified as internal ribosome entry sites in col. 16, lines 35-38). Thus, the patent teaches, or renders obvious, the use of IRES elements in the HCV clones.

Rice also teaches that the clones, and cells comprising those clones, may be used in methods of for screening for agents capable of modulating HCV replication in vitro. Col. 13, lines 49-51 and col. 38, lines 30-38. The patent identifies several HCV genes that may be used as targets in these methods. Cols. 25-26. Such targets include the HCV C protein, the E1 or E2 glycoproteins, and the NS2, NS3, NS4 or NS5 proteins. Id. Thus, the patent teaches the use of these proteins as targets for anti-HCV therapeutics.

Rice also describes a screening method wherein a cell line is contacted with a candidate agent, and tested for an increase or a decrease in the level of HCV activity. Col. 14, lines 5-24. The patent goes on to teach "a further method" of screening for anti-HCV replication agents, thereby indicating that the activities being screened for in the first method include replication. Col. 25, lines 25-27. The patent teaches that where the HCV clone used includes a heterologous gene associated with an expression control sequence, the testing for the level of HCV activity comprises measuring the level of the marker protein. Col. 14, lines 18-24. In such a case, the patent indicates that a decrease in the level of expression of the heterologous gene after contact with the agent indicates that ability of the agent to inhibit HCV replication. Col. 14, lines 32-36. In such a method, it would be apparent that the contacting step could involve the culturing of the cells in the presence of the test agent. Therefore, the patent anticipates, or renders obvious, the methods of claims 1, 4, and 8.

Claim 57 teaches a method of determining the resistance to a drug in a patient. For the purposes of this rejection, the claim is being read as though it was measuring the viral resistance to the drug in an in vivo test in the patient. The Rice patent describes a method of screening for agents capable of modulating HCV replication in vivo and in vitro. Col. 13, lines 49-61. The in vivo embodiment tests the level of HCV infectivity or activity in an animal before and after administration of the agent. Id. The patent also indicates that a decrease in the level of HCV infection after administration of the agent indicates that the agent has the ability to inhibit HCV infection or activity. It would be obvious to one of ordinary skill in the art that if there were no change, or an increase in HCV activity the agent would be ineffective against or an agonist to HCV infection. The patent also teaches that the cells and animals of the patent may be used to examine the emergence of HCV variant resistant to existing and novel therapeutics. Col. 38, lines 9-12. The patent states that such resistance may develop over time. In view of this information, it would therefore have been obvious to one of ordinary skill in the art to use the method used to screen for agents capable of inhibiting HCV to screen for the development of resistance against such therapeutics in a patient.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. **(Prior Rejection-Maintained)** Claims 1, 4, 8, 55, and 57 were rejected in the prior action under the judicially created doctrine of obviousness-type double patenting as being unpatentable over either claims 1, 4, 7-11, 13,14,46-49,51-53,70-73, and 78-83 of U.S. Patent 5,837,464 in view of Lu et al. and Wang et al., or claims 1,2,18,24-27, and 30-42 of U.S. Patent No. 6,242,187, in view of Lu et al. or Wang et al. In the prior office action, these claims were rejected under both 35 U.S.C. 103(a) and for Obviousness Type Double Patenting based on the '464 patent in view of Lu and Wang, and for obviousness type double patenting over the '187 patent in view of Lu and Wang. In Amend. F, the applicant traversed the 35 U.S.C. 103(a) rejection on the grounds that the '494 patent was not available as prior art under 35 U.S.C. 103(a) because of common ownership of that patent and the presently claimed invention at the time the invention of the present application was made. While this is an effective argument against a rejection under 35 U.S.C. 103(a), it is not effective against an obviousness type double patenting rejection. The only ground for traversing the obviousness rejection in Amend. F was the common ownership. As the applicant did not provide any other arguments against finding the present claims obvious over those of the '494 patent in view of Lu and Wang, and as the same arguments apply with respect to the '187 patent in view of Lu and Wang, the double patenting rejection is maintained for the reasons stated in the 35 U.S.C. 103(a) and double patenting rejections in the prior action.

Further, the rejections are also maintained in that it would have been obvious to one of ordinary skill in the art to combine the methods taught in Rice et al., U.S. Patent 6,127,116 (described above) and either of the prior Capon et al patents to achieve the methods of the present claims. The motivation to combine these references would be to develop an effective method of identifying anti-HCV therapeutics and methods of ensuring the continued efficacy of such therapeutics. There would have been a reasonable expectation of success in the combination as each of the Capon references teaches the efficacy of the methods in assays for therapeutics against HBV and HIB, and because Rice teaches a similar, if not identical, method using HCV. As the methods were effective for use in assays surrounding other viral infections as taught by the Capon references, and as like methods were also effective in methods against HCV infections, one of ordinary skill in the art would have had a reasonable expectation of success in the use of the methods of the prior Capon patents to identify therapeutics to, and to assay for resistance to such therapeutics, in HCV.

Conclusion

13. No Claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
October 28, 2002

JAMES HOUSEL 11/3/02
SUPERVISORY PATENT EXAMINER
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